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Differentiated thyroid cancer in children and adolescents

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Abstract *Introduction:* There have been only a few studies on differentiated childhood thyroid cancer (DTC) in children and adolescents. *Methods:* We analyzed the characteristics of DTC with respect to age, gender and histology in 114 patients under 18 years of age. In a questionnaire-based survey, data of 114 patients, aged between 3 years and 18 years, was collected from 65 clinical institutions in Germany. Characteristics of 80 females and 34 males were evaluated, and the prognostic effect of age, gender, histology, multicentric growth, tumor stage and N-status on distant metastases was tested using multivariate discriminant analysis. Between-group comparison was performed using student t-test and chi-squared test. *Results:* The incidence of DTC in females was higher than in males with a peak of female:male ratio at puberty, which was more pronounced in children with papillary thyroid cancer, but not with follicular thyroid cancer. Papillary thyroid cancer was associated with more advanced disease (P = 0.009), more lymph-node involvement (P = 0.007) and more distant metastases (P = 0.02) compared with follicular thyroid cancer. Multivariate analysis showed advanced tumor stage as the only significant factor (P = 0.02) associating with distant metastasis. *Conclusion:* It can be concluded that in children and adolescents: 1. The incidence of papillary thyroid cancer is higher in females than males, with a peak at puberty. 2. The only significant factor associated with distant metastases is the advanced tumor stage. 3. Childhood thyroid cancer is frequently associated with lymph-node involvement, distant metastases and advanced tumor stage. 4. Papillary childhood thyroid cancer is more aggressive than follicular type.

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Introduction

Since the outbreak of childhood thyroid cancer in the area around Chernobyl following the reactor accident of 1986 [1, 2], there has been several studies on childhood thyroid cancer. In addition, there are several reports of an increased number of this malignancy in Sweden [3], England and Wales [4]. The characteristics of thyroid cancer in children with respect to different prognostic factors are, however, still poorly understood.

Because tumor biology and pathway of metastases in different histological types of thyroid cancer are different [5–7], we analyzed the age-specific characteristics of differentiated thyroid cancer (DTC) in 114 children and adolescents with respect to gender and histology.

Methods

This retrospective analysis was initiated by participants of the Multicentric Prospective Project: "Malignant Endocrine Tumors in Children and Adolescents". The aim of this project, supported by the German Society for Pediatric Oncology and Hematology and Children's Cancer Registry at the University of Mainz, was to design a prospective multicentric therapy study for childhood thyroid cancer, using the results of the present retrospective analysis.

Data of DTC was collected in a survey from 65 widely dispersed centers in Germany. A detailed questionnaire sent to the centers included questions on age, gender, histology, multicentric tumor, tumor stage, treatment and outcome [8]. A total of 114 patients between 3 years and 18 years of age, followed up after treatment for DTC between 1980 and 1993 in these centers, were the subject of our study.

Characteristics of 80 females and 34 males with respect to age at diagnosis, histology, multicentric growth, tumor stage, lymph-node involvement and distant metastases are depicted in Table 1. Only patients with well-documented histology, surgical and biochemical records, with a follow-up time of at least 1 year, were included in this study. Mixed papillary-follicular thyroid cancers were consid-

Table 1 Characteristics of differentiated thyroid cancer in 80 females and 34 males

	Females (n = 80) No. (%)	Males (n = 34) No. (%)	P-value
PTC	61 (0.76)	28 (0.82)	0.51
Stage pT4	23 (0.29)	10 (0.29)	1.00
Stage N1	41 (0.51)	18 (0.53)	0.89
Stage M1	18 (0.22)	11 (0.32)	0.08

P values are derived from results of chi-squared test (significance level = 0.05). *PTC*, papillary thyroid cancer

Table 2 Characteristics of 114 children and adolescents with differentiated papillary and follicular thyroid cancer

	Papillary (n = 89) No. (%)	Follicular (n = 25) No. (%)	P-value
Girls	61 (0.69)	19 (0.76)	0.48
Stage pTb	20 (0.22)	3 (0.12)	0.25
Stage pT4	31 (0.35)	2 (0.08)	0.009
Stage N1	52 (0.58)	7 (0.28)	0.007
Stage M1	27 (0.30)	2 (0.08)	0.02

P values are derived from results of chi-squared test (significance level = 0.05)

ered as papillary thyroid cancer (PTC) (according to the WHO classification). Patients with undifferentiated thyroid cancer (one case), medullary thyroid cancer (seven cases), and history of radiation exposure (one case) were excluded from this study. All tumor stages were reclassified according to UICC 1987. Lymph-node involvement and distant metastases were assessed in all patients by clinical examination, ultrasound of the neck, iodine-131 whole-body scan, thyroglobulin and chest X-ray.

Indeed, all children underwent thyroidectomy and iodine-131 treatment; however, due to different treatment and diagnostic workup used in follow-up in different centers, we did not perform further analysis regarding outcome of patients.

Statistical analyses were performed using a Macintosh computer and StatView program (Abacus Concepts for Macintosh). Between-group comparison was performed using Student t-test and chi-squared test.

Univariate and multivariate discriminant analyses were carried out to test the influence of the prognostic factors age, gender, histological type, multicentric growth, tumor stage and lymph-node category on distant metastases at staging. A *P* value of less than 0.05 was considered to be significant.

Results

The characteristics of 80 girls and 34 boys included in our study are summarized in Table 1. Mean age was not significantly different ($P = 0.14$) between girls (13.6± 3.7 years) and boys (12.4±4.0 years). There was no significant difference of histological type, tumor stage and lymph-node involvement between girls and boys (Table 1). Seventy-nine percent of boys and 75% of girls had cancer confined to only one site of thyroid ($P = 0.65$), whereas the remaining 15% and 23%, respectively, had bilateral tumor or tumor localized in the isthmus ($P = 0.04$). Male gender

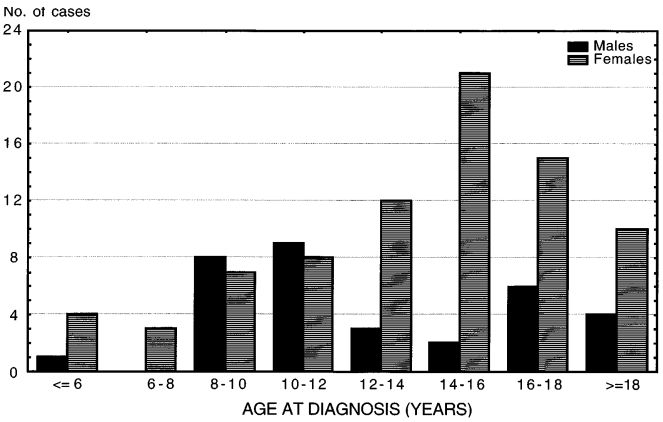

Fig. 1 Distribution of differentiated thyroid cancer in children and adolescents; breakdown by gender (n = 114)

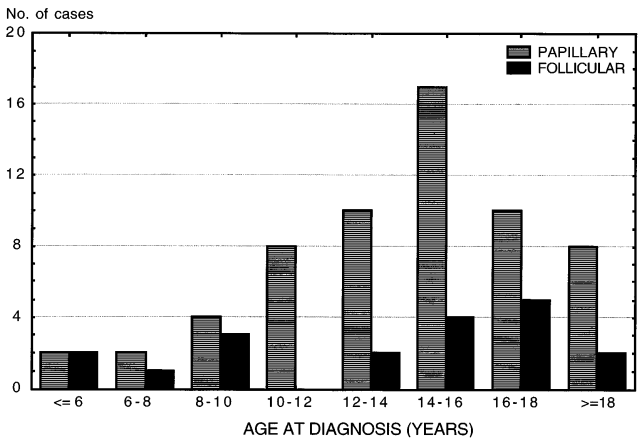

Fig. 2 Distribution of differentiated thyroid cancer in females; breakdown by histology (n = 80)

was associated with a higher risk for distant metastasis; however, the statistical analysis failed to reveal the significant effect of gender on metastasis ($P = 0.08$).

PTC was present in 89 (78%) children. The remaining 25 (22%) suffered from follicular thyroid cancer (FTC), of whom only two had advanced disease in stage pT4, and distant metastases (Table 2). PTC was associated with a significantly higher frequency of advanced disease (35% vs 8%), lymph-node involvement (58% vs. 28%) and distant metastases (30% vs 8%) than FTC (Table 2).

In general, the incidence of thyroid cancer in females was higher than in males, which was more pronounced at puberty. The frequency of tumor revealed an increase with age (Fig. 1) in females (<16 years) which was more pronounced in females with PTC than FTC (Fig. 2).

The overall frequency of metastases was 25%. The most powerful factor associating (Table 3) with metastases (multivariate analysis) was advanced tumor stage (P = 0.02), which was more pronounced (P = 0.002) in children with PTC than FTC. Younger children tend to have more metastases (Table 3), but the statistical analysis just failed to reach the level of significance (P = 0.08).

Table 3 Influence of age, gender, histology, multicentric growth, tumor stage and lymph node involvement on frequency of metastases at staging in children and adolescents with differentiated thyroid cancer (multivariate discriminant analysis). *PTC* papillary thyroid cancer; *FTC* follicular thyroid cancer

Factors	No. of patients	No. of metastases	*P*-value
Age	114	29	0.08
Females	80	18	
Males	34	11	0.38
PTC	89	27	0.20
FTC	25	2	
pTa	62	21	0.39
pTb	18	7	
pT1	7	2	
pT2	32	6	
pT3	11	2	
pT4	30	19	0.02
N0	26	3	
N1	55	26	0.28

Discussion

Several kinds of human malignancies are supposed to be influenced by endogenous hormones [9, 10]. The frequency of these hormone-dependent tumors is reported to be different between females and males [9]. This effect is clearly demonstrated for breast cancer, the etiology of which is related to hormonal factors [11, 12]. Thyroid cancer is one of those malignancies, which predominantly occurs in females [9], suggesting that hormonal determinants are involved in the pathogenesis of this malignancy. A review of the literature reveals several studies supporting this hypothesis. Pregnant women are shown to have increased circulating levels of thyroid-stimulating hormone (TSH) after the end of the first trimester [13, 14]. Indeed, this finding may apply only to iodine-deficient areas [15]. However, Germany remains one of the few countries with no mandatory iodine prophylaxis, with an overall prevalence of endemic iodine-deficiency goiter of about 50% [7]. TSH is the principal hormone regulating the growth and function of the thyroid gland and has been shown to induce thyroid cancer in animal experiments [16–18]. Thus, all factors enhancing TSH secretion may be associated with an increased risk of thyroid cancer [19].

Hallquist et al. demonstrated, in a case-control study on 180 patients aged 20–70 years and 360 controls, that the history of pregnancy was associated with increased risk of PTC [20]. In another epidemiological case-control study in women aged 40 years and younger, pregnancy increased the risk of thyroid cancer [10]. After excluding women with underlying thyroid disease and those whose first pregnancy ended in miscarriage, there was an increase in risk of thyroid cancer with an increasing total number of pregnancies [10].

Endogenous hormones can also influence the thyroid tissue directly. Imai et al. studied the reactions of sex-hormone (estrone, estradiol, estriol and testosterone) antisera in 109 cancerous and 80 normal and benign thyroid tissue specimens immunhistochemically [21]. They found that endogenous estradiol was located in thyroid cancers more frequently in females (56%) than in males (33%). Estrogen-binding activity in the cells was not only present in thyroid cancers, but also in normal and benign thyroid tissues [21].

Our analysis demonstrated that the age-specific increase of thyroid cancer in females is related to puberty. The incidence of thyroid cancer at puberty was remarkably higher in females than in males, whereas the female:male ratio in children and adolescents, before and after puberty, was comparable to that in adults. Further analysis in our study indicated that this gender-specific excess of thyroid cancer was present only in females with PTC, but not with FTC (Fig. 2). It is well known that growth spurt and the appearance of secondary sex characteristics at puberty occur concomitantly with an increase of sex hormones [22]. Thus, the present study supports the hypothesis of involvement of sex hormones in the pathogenesis of PTC but not FTC.

Males tend to have more metastases than females (Table 1). However, statistical results just failed ($P = 0.08$) to reach the level of significance (Table 1).

Of 114 (52%) children, 59 had lymph-node metastases at diagnosis, which is more than that reported in children (44%) from France and Italy [23]. In our study, lymph-node involvement in children with PTC (58%) was significantly higher than in those with FTC (28%), but was comparable to results from Belarus (65%) [23]. The role of lymph-node involvement on prognosis of patients with DTC is controversial [5, 24]. In a recent study, we demonstrated an adverse prognostic effect of lymph-node involvement in patients with advanced differentiated thyroid cancer [7]. Indeed, the univariate analysis in the present study demonstrated a higher frequency of distant metastases in lymph-node positive patients ($P = 0.004$). Multivariate analysis, however, disclosed this effect to be present only in those children with advanced disease. This finding underscores the prognostic effect of lymph-node involvement in childhood DTC only in the case of a co-correlation with advanced disease.

Twenty-five percent of children in our study had distant metastases, which was similar to results in children from France and Italy (24%) [23]. Indeed, these data demonstrate a higher frequency of distant metastases in children from Western Europe compared with those reported in children from Belarus (9%). However, the frequency of distant metastases is due to the limited availability of iodine-131 scan in cases from Belarus presumably underestimated.

In agreement with results from France and Italy [23], extrathyroidal tumor invasion was present in approximately one-third (32% vs 29%) of the children, mostly in those with PTC (35%) compared with FTC (8%). In comparison, children from Belarus tend to have a higher frequency (48%) of extrathyroidal tumor invasion [23].

A total of 78% of tumors were of papillary type compared with only 22% follicular type. In agreement, the pro-

portion of PTC in children from England and Wales [25] was comparable (77%) with our results. Similar data (76% PTC) were also reported in children with DTC from France and Italy [23]. Thus, concordant results of these three studies suggest a lower incidence of PTC in children from Western Europe (representing non-radiation-exposed children) compared with childhood thyroid cancer from Belarus (representing mostly radiation-induced thyroid cancer). In the first report of thyroid cancer arising after Chernobyl, all tumors were of PTC type [1, 2]. Of among 84 childhood thyroid cancers removed in Minsk between 1991 and 1992, 83 were found to be PTC and only one a medullary thyroid cancer [26].

In contrast, the review of the literature shows a higher incidence of FTC (10–17%) among radiation-induced thyroid malignancies [27–31] than in studies from Belarus. The lower incidence of FTC in children from Belarus could be due to a longer latent period of this type of DTC after radiation exposure. Nikiforov reported on the first case of FTC diagnosed in the exposed population of children from Chernobyl area after a 6.5-year latent period, compared with 4 years of minimal latency for PTC [32].

The lower incidence of FTC among radiation-induced childhood thyroid carcinoma from Belarus could also be due to different effects of radiation exposure by iodine-131 than external radiation.

Compared with PTC, in the present study, FTC results in a lower incidence of extrathyroidal tumor infiltration, lymph-node involvement and a lower number of distant metastases, suggesting this type of DTC to be less aggressive than PTC. Indeed, FTC is believed to have a less favorable prognosis than PTC [33–36]. However, this could be mostly related to the typical presentation of this malignancy in older patients and co-correlation with more advanced disease rather than tumor histology [37].

To our knowledge, there are only a few studies dealing with prognosis of DTC in children with respect to histology. In a study of 93 children with DTC from Sloan-Kettering Cancer Center, La Quaglia et al. report on a lower rate of recurrence in children with FTC than with papillary or papillary–follicular carcinomas [38]. In the multivariate analysis, the only powerful significant factor affecting the time to recurrence was the histological type ($P < 0.01$) [38]. Schlumberger et al. also reported on a lower relapse rate for FTC in a series of 72 children with DTC under 16 years of age with a median follow-up time of 13 years [39]. Thus, concerning these studies, the "U-shaped frequency distribution of recurrent disease" reported by Mazzaferri [37] with significantly more recurrences before age 20 years and after age 60 years ($P < 0.0001$) in patients with differentiated thyroid cancer may only apply to papillary type of this malignancy.

It can be concluded that:

1. The incidence of papillary thyroid cancer is higher in females than males, with a peak at puberty.
2. The only significant factor associated with distant metastases in children is the advanced tumor stage.
3. Childhood thyroid cancer is frequently associated with lymph-node involvement, distant metastases and advanced tumor stage.
4. In children, papillary childhood thyroid cancer is more aggressive than follicular type.

References

1. Baverstock K, Egloff B, Pinchera A, Ruchti C, Williams D (1992) Thyroid cancer after Chernobyl. Nature 359: 21–22
2. Kazakov VS, Demidchik EP, Astakhova LN (1992) Thyroid cancer after Chernobyl. Nature 359: 21
3. Peterson B, Adami HO, Wilander E, Coleman MP (1991) Trends in thyroid cancer incidence in Sweden, 1958–1981. Int J Cancer 48: 28–33
4. dos Santos Silva I, Swerdlow AJ (1993) Sex differences in the risks of hormone-dependent cancers. Am J Epidemiol 138: 10–28
5. Franssila K (1973) Is the differentiation between papillary and follicular thyroid cancer valid? Cancer 32: 853–864
6. Nemec J, Zamrazil V, Pohunkova D, Zeman V, Röhling S (1979) Mode of spread of thyroid cancer. Oncology 36: 232–235
7. Farahati J, Reiners C, Stuschke M, Müller SP, Stüben G, Sauerwein W, et al. (1996) Differentiated thyroid cancer: the impact of adjuvant external radiotherapy in patients with perithyroidal tumor infiltration (stage pT4). Cancer 77: 172–180
8. Parlowsky T, Bucsky P, Hof M, Kaatsch P (1996) Malignant endocrine tumors in childhood and adolescence – results of a retrospective analysis. Klin Padiatr 208: 205–209
9. Henderson BE, Ross RK, Pike MC, Casagrande JT (1982) Endogenous hormones as a major factor in human cancer. Cancer Res 42: 3232–3239
10. Preston-Martin S, Pike MC, Ross RK, Jones PA, Henderson BE (1990) Increased cell division as a cause of human cancer. Cancer Res 50: 7415–7421
11. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG (1983) 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. Nature 303: 767–770
12. Bernstein L, Ross RK, Pike MC, Casagrande JT, Henderson BE (1989) Urinary estrogens and male-to-female breast cancer ratios. Int J Cancer 44: 954–956
13. Osathanondh R, Tulchinsky D, Chopra IJ (1976) Total and free thyroxine and triiodthyronine in normal and complicated pregnancy. J Clin Endocrinol Metab 42: 98–104
14. Glinoer D (1996) Maternal and neonatal thyroid function in mild iodine deficiency. In: Nauman J, Glinoer D, Braverman LE, Hostalek U (eds) The thyroid and iodine. Schattauer, Stuttgart, pp 129–143
15. Reiners C (1991) Schilddrüsenfunktion und -funktionsparameter in der Schwangerschaft. Med Welt 42: 14–20
16. Lindsay SL, Nichols CW, Chaikoff IL (1966) Induction of benign and malignant thyroid neoplasms in the rat. Arch Pathol 81: 308–316
17. Nadler NJ, Mandavia M, Goldberg M (1970) The effect of hypophysectomy on experimental production of rat thyroid neoplasms. Cancer Res 30: 1909–1911
18. Christov K (1975) Thyroid cell proliferation in rats and induction of tumors by x-rays. Cancer Res 35: 1256–1261
19. Williams ED (1979) The aetiology of thyroid tumors. Clin Endocrinol Metab 8: 193–207
20. Hallquist A, Hardell L, Degerman A, Boquist L (1994) Thyroid cancer: reproductive factors, previous diseases, drug intake, family history and diet. A case-control study. Eur J Cancer Prev 3: 481–488
21. Imai Y, Yamakawa M, Matsuda M, Kasajima T (1989) Endogenous sex hormone and estrogen binding activity in thyroid cancer. Histol Histopathol 4: 39–45

22. Caufriez A (1997) The pubertal spurt: effects of sex steroids on growth hormone and insulin-like growth factor I. Eur J Obstet Gynecol Reprod Biol 71:215–217
23. Pinchera A, Demidchik EP (1996) Development of optimal treatment and preventive measures for radiation-induced childhood thyroid cancer. In: Joint study project No. 4. Final report. Luxemburg: office for official publications of the European Communities, pp 19–22
24. Tubiana M, Haddad E, Schlumberger M, Hill C, Rougier P, Sarrazin D (1985) External radiotherapy in thyroid cancers. Cancer 55:2062–2071
25. Harach HR, Williams ED (1995) Childhood thyroid cancer in England and Wales. Br J Cancer 72:777–783
26. Nikiforov YE, Gnepp DR (1994) Pediatric thyroid cancer after the Chernobyl disaster: pathomorphologic study of 84 cases (1991–1992) from the republic of Belarus. Cancer 74:748–766
27. Greenspan FS (1977) Radiation exposure and thyroid cancer. JAMA 237:2089–2091
28. Spitalnik PF, Straus FH (1978) Patterns of human thyroid parenchymal reaction following low-dose childhood irradiation. Cancer 41:1098–1105
29. Schneider AB, Pinsky S, Bekerman C, Ryo UY (1980) Characteristics of 108 thyroid cancers detected by screening in a population with a history of head and neck irradiation. Cancer 46:1218–1227
30. DeGroot LJ, Reilly M, Pinnameneni K, Refetoff S (1983) Retrospective and prospective study of radiation-induced thyroid disease. Am J Med 74:852–862
31. Fjalling M, Tisell LE, Carlsson S, Hansson G, Lindberg LM, Oden A (1986) Benign and malignant thyroid nodules after neck irradiation. Cancer 58:1219–1224
32. Nikiforov YE, Heffes CS, Korzenko AV, Fagin JA, Gnepp DR (1995) Characteristics of follicular tumors and nonneoplastic thyroid lesions in children and adolescents exposed to radiation as a result of the Chernobyl disaster. Cancer 76:900–909
33. Kerr DJ, Burt AD, Boyle P, Mac Farlane GJ, Storer AM, Brewin TB (1986) Prognostic factors in thyroid tumors. Br J Cancer 54:475–482
34. Tennvall J, Biorklund A, Moller T, Ranstam J, Akerman M (1985) Prognostic factors of papillary, follicular and medullary carcinomas of the thyroid gland. Retrospective multivariate analysis of 216 patients with a median follow-up of 11 years. Acta Radiol Oncol Radiat Phys Biol 24:17–24
35. Tubiana M, Haddad E, Schlumberger M, Hill C, Rougier P, Sarrazin D (1985) External radiotherapy in thyroid cancers. Cancer 55:2062–2071
36. Wanebo J, Andrew W, Kaiser D (1981) Thyroid cancer: some basic considerations. Am J Surg 142:472–479
37. Mazzaferri EL (1991) Radioiodine and other treatment and outcomes. In: Braverman LE, Utiger RD (eds) The thyroid, 6th edn. Lippincott, Philadelphia, pp 1138–1165
38. La Quaglia MP, Corbally MT, Heller G, Exelby PR, Brennan MF (1988) Recurrence and morbidity in differentiated thyroid carcinoma in children. Surgery 104:1149–1156
39. Schlumberger M, De Vathaire F, Travagli JP, Vassal G, Lemerle J, Parmentier C, et al. (1987) Differentiated thyroid carcinoma in childhood: long term follow-up of 72 patients. J Clin Endocrinol Metab 65:1088–1094